



## **Esketamine (Spravato®)**

### **INDICATIONS AND USAGE**

SPRAVATO is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults **(approved March 5, 2019)**.

#### Limitations of Use

SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

### **Black Box Warning**

#### Sedation

Patients are at risk for sedation after administration of SPRAVATO

#### Dissociation

Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO.

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

#### Abuse and Misuse

SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS.

#### Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of

suicidal thoughts and behaviors. SPRAVATO is not approved in pediatric patients.

### **LIST PRICE**

56 mg dose = \$590

84 mg dose = \$885

### **CLINICAL PHARMACOLOGY**

#### Mechanism of Action

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Compared to the R-enantiomer, esketamine has a higher affinity for the NMDA receptor. The precise mechanism by which esketamine exerts its antidepressant effect is unknown. Proposed mechanisms of ketamine's antidepressant action include NMDA receptor modulation, AMPA receptor activation, GABAergic interneuron disinhibition, direct effects of its hydroxyl-norketamine (HNK) metabolites, and numerous downstream actions.

#### Pharmacodynamics

##### *Cardiac Electrophysiology*

The effect of SPRAVATO (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. A large increase in heart rate (i.e. >10 bpm) was observed in both intranasal and intravenous esketamine treatment groups. **The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeutic dose of esketamine.**

#### Pharmacokinetics

The mean absolute bioavailability is approximately 48% following nasal spray administration.

The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session.

Mean terminal half-life ranges from 7 to 12 hours

Esketamine is primarily metabolized to nor-esketamine via CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. Nor-esketamine is metabolized via CYP-dependent pathways; certain metabolites undergo glucuronidation. **Nor-esketamine is also a NMDA receptor antagonist but has less affinity for the receptor than does esketamine.**

Less than 1% of a dose of nasal esketamine is excreted as unchanged drug in urine. Following intravenous or oral administration, esketamine-derived metabolites were primarily recovered in urine ( $\geq 78\%$  of a radiolabeled dose) and to a lesser extent in feces ( $\leq 2\%$  of a radiolabeled dose).

No significant differences in the PK of SPRAVATO nasal spray were observed for sex and total body weight (>39 to 170 kg) based on population PK analysis. There is no clinical experience with SPRAVATO nasal spray in patients on renal dialysis or with severe (Child-Pugh class C) hepatic impairment. There is no dose adjustment for body weight, sex, renal impairment, hepatic impairment or nasal congestion.

## **DOSAGE AND ADMINISTRATION**

### **Important Considerations Prior to Initiating and During Therapy**

SPRAVATO must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of SPRAVATO and post-administration observation under supervision.

#### Blood Pressure Assessment Before and After Treatment

Assess blood pressure prior to dosing with SPRAVATO.

If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATO treatment in patients with TRD. Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk.

After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes (which corresponds with the  $C_{max}$ ) and subsequently as clinically warranted.

If blood pressure is decreasing and the patient appears clinically stable for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor.

#### Food and Liquid Intake Recommendations Prior to Administration

Because some patients may experience nausea and vomiting after administration of SPRAVATO, advise patients to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.

#### Nasal Corticosteroid or Nasal Decongestant

Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before SPRAVATO.

### Recommended Dosage

Administer SPRAVATO in conjunction with an oral antidepressant (AD).

The recommended dosage for SPRAVATO is shown in Table 1. Dosage adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

Table 1: Recommended Dosage for SPRAVATO

<b>Induction Phase</b>	<b><u>Weeks 1 to 4:</u></b> <b>Administer twice per week</b> <b>Day 1 starting dose: 56 mg</b> <b>Subsequent doses: 56 mg or 84 mg</b>
<b>Maintenance Phase</b>	<b><u>Weeks 5 to 8:</u></b> Administer once weekly 56 mg or 84 mg <b><u>Week 9 and after:</u></b> Administer every 2 weeks or once weekly* 56 mg or 84 mg

\*Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

### Administration Instructions

SPRAVATO is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. **Each nasal spray device delivers two sprays containing a total of 28 mg esketamine.** To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.

### Post-Administration Observation

During and after SPRAVATO administration at each treatment session, observe the patient for at least 2 hours until the patient is safe to leave. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

### Missed Treatment Session(s)

If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgment, consider returning to the patient's previous dosing schedule (i.e., every two weeks to once weekly, weekly to twice weekly; see Table 1).

## **CONTRAINDICATIONS**

Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation.

History of intracerebral hemorrhage

Hypersensitivity to esketamine, ketamine, or any of the excipients.

## **WARNINGS AND PRECAUTIONS**

### **Sedation**

In clinical trials, 49% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer's Alertness/Sedation scale (MOAA/s) and 0.3% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/s score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

### **Dissociation**

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (distortion of time, space, illusions), derealization and depersonalization. Sixty-one (61%) to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale. Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. In clinical trials, dissociation was transient and occurred on the day of dosing.

**Abuse and Misuse**

SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

**SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)**

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

The following information is from [www.SPRAVATOREMS.com](http://www.SPRAVATOREMS.com)

**How does my Healthcare Setting become certified in the SPRAVATO REMS?**

Step 1: Designate an Authorized Representative to oversee implementation and compliance with the REMS requirements

Step 2: Review the following materials: a) SPRAVATO REMS Fact Sheet; b) SPRAVATO Prescribing Information; c) SPRAVATO Medication Guide; d) SPRAVATO Instructions for Use

Step 3: Complete and submit (online or by fax) the SPRAVATO REMS Healthcare Setting Enrollment Form to the REMS

**How does my Pharmacy become certified in the SPRAVATO REMS?**

Step 1: Designate an Authorized Representative to oversee implementation and compliance of the SPRAVATO REMS requirements

Step 2: Review the following materials: a) SPRAVATO REMS Fact Sheet; b) SPRAVATO Prescribing Information; c) SPRAVATO Medication Guide; d) SPRAVATO Instructions for Use

Step 3: Complete and submit (online or by fax) the SPRAVATO REMS Pharmacy Enrollment Form to the REMS

**How do I (Patients) enroll in the SPRAVATO REMS?** These are the steps to take in partnership with your healthcare provider:

Step 1: Read the SPRAVATO Medication Guide and Instructions for Use. Your healthcare provider will review specific risk and safety information of SPRAVATO with you and describe how to use the product.

Step 2: Ask your healthcare provider any questions you have about taking SPRAVATO and about the SPRAVATO REMS.

Step 3: Make sure you understand:

How to enroll and take part in the SPRAVATO REMS

The benefits and risks of SPRAVATO

That each time you receive SPRAVATO

You will need to use SPRAVATO nasal spray yourself under direct observation of a healthcare provider in a healthcare setting, such as a doctor's office, clinic, or hospital

You will be monitored by a healthcare provider for at least 2 hours; the healthcare provider will then decide when you are ready to leave the healthcare setting.

After treatment with SPRAVATO, **do not** drive, operate heavy machinery, or do anything where you need to be completely alert until the next day following a restful sleep.

Step 4: Together with your healthcare provider complete and sign the SPRAVATO REMS Patient Enrollment Form. Your healthcare provider will fill out most of the enrollment form for you and will send the form to SPRAVATO REMS.

### **Suicidal Thoughts and Behaviors in Adolescents and Young Adults**

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

### **Increase in Blood Pressure**

SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 4 hours.

**Approximately 8% to 17% of SPRAVATO-treated patients and 1% to 3% of placebo-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations.** The mean placebo-adjusted increases in systolic and diastolic blood pressure over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants.

SPRAVATO is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks. Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO administration (as a general guide: >140/90 mmHg) a decision to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.



BP should be monitored for at least 2 hours after SPRAVATO administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs).

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

## **Cognitive Impairment**

### Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

### Long-Term Cognitive Impairment

Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

## **Impaired Ability to Drive and Operate Machinery**

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive. The effects of SPRAVATO 84 mg were comparable to placebo at 6 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of the studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions.

Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and

motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO.

### Ulcerative or Interstitial Cystitis

Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

### Embryo-fetal Toxicity

Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

## ADVERSE REACTIONS

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence  $\geq$  5% and at least twice that of placebo nasal spray plus oral AD) were **dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.**

*Adverse reactions occurring in  $\geq$  2% of TRD patients treated with SPRAVATO + oral AD at any dose and at a greater rate than patients treated with placebo nasal spray + oral AD*

	<b>SPRAVATO + oral AD (n = 346)</b>	<b>Placebo + oral AD (n = 222)</b>
<b>Cardiac disorders</b>		
<b>Tachycardia</b>	6 (2%)	1 (0.5%)
<b>Ear and labyrinth disorders</b>		

	<b>SPRAVATO + oral AD (n = 346)</b>	<b>Placebo + oral AD (n = 222)</b>
<b>Vertigo</b>	<b>78 (23%)</b>	<b>6 (3%)</b>
<b>Gastrointestinal disorders</b>		
<b>Constipation</b>	11 (3%)	3 (1%)
<b>Diarrhea</b>	23 (7%)	13 (6%)
<b>Dry mouth</b>	19 (5%)	7 (3%)
<b>Nausea</b>	<b>98 (28%)</b>	<b>19 (9%)</b>
<b>Vomiting</b>	<b>32 (9%)</b>	<b>4 (2%)</b>
<b>General disorders and administration site conditions</b>		
<b>Feeling abnormal</b>	12 (3%)	0 (0%)
<b>Feeling drunk</b>	<b>19 (5%)</b>	<b>1 (0.5%)</b>
<b>Investigations</b>		
<b>Blood pressure increased</b>	<b>36 (10%)</b>	<b>6 (3%)</b>
<b>Nervous system disorders</b>		
<b>Dizziness</b>	<b>101 (29%)</b>	<b>17 (8%)</b>
<b>Dysarthria</b>	15 (4%)	0 (0%)
<b>Dysgeusia</b>	66 (19%)	30 (14%)
<b>Headache</b>	70 (20%)	38 (17%)
<b>Hypoesthesia</b>	<b>63 (18%)</b>	<b>5 (2%)</b>
<b>Lethargy</b>	<b>37 (11%)</b>	<b>12 (5%)</b>
<b>Mental impairment</b>	11 (3%)	2 (1%)
<b>Sedation</b>	<b>79 (23%)</b>	<b>21 (9%)</b>
<b>Tremor</b>	12 (3%)	2 (1%)
<b>Psychiatric disorders</b>		
<b>Anxiety</b>	<b>45 (13%)</b>	<b>14 (6%)</b>
<b>Dissociation</b>	<b>142 (41%)</b>	<b>21 (9%)</b>
<b>Euphoric mood</b>	15 (4%)	2 (1%)

	<b>SPRAVATO + oral AD (n = 346)</b>	<b>Placebo + oral AD (n = 222)</b>
<b>Insomnia</b>	29 (8%)	16 (7%)
<b>Renal and urinary disorders</b>		
<b>Pollakiuria</b>	11 (3%)	1 (0.5%)
<b>Respiratory, thoracic and mediastinal disorders</b>		
<b>Nasal discomfort</b>	23 (7%)	11 (5%)
<b>Oropharyngeal pain</b>	9 (3%)	5 (2%)
<b>Throat irritation</b>	23 (7%)	9 (4%)
<b>Skin and subcutaneous tissue disorders</b>		
<b>Hyperhidrosis</b>	14 (4%)	5 (2%)

## **DRUG INTERACTIONS**

Central Nervous System Depressants Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

### Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

### Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

## **Use in Specific Populations**

### Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at <https://womensmentalhealth.org/clinical-and-researchprograms/>

*pregnancyregistry/antidepressants/.*

#### Risk Summary

SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

#### Lactation

Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity. Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

#### Females and Males of Reproductive Potential

##### Contraception

Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman. However, it is not clear how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO.

#### Pediatric Use

The safety and effectiveness of SPRAVATO in pediatric patients have not been established.

#### Geriatric Use

Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO, (n =1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age. The mean esketamine C<sub>max</sub> and AUC values were higher in elderly patients compared with younger adult patients.

#### Hepatic Impairment

The mean esketamine AUC and  $t_{1/2}$  values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

## **CLINICAL STUDIES**

**TRANSFORM-2** (NCT02418585) is a four-week, randomized, placebo-controlled, double-blind, multicenter, phase 3 trial that compares the effect of treatment with a newly initiated daily oral antidepressant (AD) plus flexible doses of intranasal SPRAVATO versus newly initiated daily oral AD plus intranasal placebo.

The study was conducted in adult patients 18 to < 65 years of age with a DSM-5 diagnosis of **single episode ( $\geq 2$  years)** or **recurrent major depressive disorder without psychotic features**. Inclusion criteria also included an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score  $\geq 34$  and additional requirements which are listed below in the description of the screening/prospective observational phase.

**Exclusion criteria included the following: previous nonresponse of depressive symptoms to esketamine or ketamine in the current MDE; previous nonresponse, in the current MDE, to all four of the oral antidepressant treatment options available for the DB induction phase (duloxetine, escitalopram, sertraline, venlafaxine XR); nonresponse to an adequate course of treatment with ECT in the current MDE; received vagal nerve stimulation or deep brain stimulation in the current MDE; current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar, or related disorders, comorbid obsessive compulsive disorder, intellectual disability, or personality disorder; homicidal ideation/intent; suicidal ideation with some intent to act within six months prior to the start of the screening/prospective observational phase; history of moderate or severe substance or alcohol use disorder.**

TRANSFORM 2 began with a 4 to 7 week screening/prospective observational phase. **Prior to entry into this phase, eligible participants were required (1) to have demonstrated documented nonresponse, per the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ) to one to no more than five antidepressant treatments in the current episode of depression and**

**(2) to have been taking a different oral AD medication at or above the minimum therapeutic dose for at least the previous two weeks.**

All antidepressant medications continued at this same dose for weeks 1 through 4 of the screening/prospective observation phase with an option to taper the antidepressants over the additional 3 weeks. Non-response was defined as  $\leq 25\%$  improvement in MADRS total score from week 1 to week 4 and a MADRS total score  $\geq 28$  at weeks 2 and 4.

Non-responders were randomized 1:1 to four weeks of DB treatment with either newly initiated daily oral AD plus flexible doses of intranasal SPRAVATO or newly initiated daily oral AD plus intranasal placebo. Under researchers' supervision, patients self-administered SPRAVATO 56 mg on day 1, then flexible doses of 56 or 84 mg on days 4, 8, 11, or 15, after which the dose remained stable. Two-thirds (66.7%) of patients were taking 84 mg by the end of the DB phase. Based on prior treatment history investigators also started open-label treatment with duloxetine, escitalopram, sertraline, or extended-release venlafaxine following a fixed titration schedule. Thirty-two (32%) of patients received SSRIs while the remaining 68% received SNRIs.

### *Results*

Participants had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. Approximately 36% of the participants had been treated with 3-5 previous antidepressant medications in the current depressive episode.

The primary efficacy measure was change from baseline (BL) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at four weeks. The MADRS is a clinician-rated, ten-item scale with a score range of 0 to 60 (higher scores indicate more severe depression). **Compared to placebo nasal spray plus a newly initiated oral AD, SPRAVATO plus a newly initiated oral AD showed statistical superiority on the primary efficacy measure (see Table 1).**

<b>Table 1: Change from BL in MADRS Total Score at Week 4</b>				
<b>Treatment Group</b>	<b>Number of Patients</b>	<b>Mean BL Score (SD)</b>	<b>LS Mean (SE) Change from BL to end of Week 4</b>	<b>LS Mean Difference (95% CI)*</b>
<b>SPRAVATO (56 mg or 84 mg) + Oral AD**</b>	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3;-0.6)
<b>Placebo nasal spray + Oral AD</b>	109	37.3 (5.7)	-15.8 (1.3)	

\*Difference (SPRAVATO + Oral AD minus Placebo nasal spray + Oral AD) in least-squares mean change from BL

\*\*SPRAVATO + Oral AD was statistically significantly superior to placebo nasal spray + oral AD

**SUSTAIN-1** (3003 Trial, NCT 02493868)

#### *Methods/Study Design*

Daly et al (2018) conducted a multi-center, double-blind, randomized withdrawal study to assess the efficacy of SPRAVATO + AD compared with an AD + PBO in **delaying relapse of depressive symptoms** in patients with TRD who were in stable remission after an induction and optimization course of SPRAVATO + AD.

Patients either directly entered the study or transferred in from the short-term trials. The study consisted of up to five phases: (1) screening/prospective observational phase (4-7 weeks) and (2) open-label induction phase (4 weeks) for direct-entry patients only; (3) optimization phase (12 weeks; open-label for direct-entry patients and double-blind for transfer-entry patients); (4) maintenance phase (variable duration; double-blind for all patients); (5) follow-up phase (2 weeks). **The study continued until a prespecified number of relapses occurred.**

At the end of the induction phase, both direct-entry and transfer-entry patients who were treatment responders ( $\geq 50\%$  reduction in MADRS total



score from baseline) entered a 12-week optimization phase. During this phase, the oral AD and study drug nasal spray (either SPRAVATO or placebo) remained constant, but the frequency of nasal spray medication was reduced to weekly for the first 4 weeks, then individualized to either once weekly or once every 2 weeks based on patient response.

The maintenance phase began at week 16 (after the induction and optimization phases). Investigators randomized (1:1) SPRAVATO plus oral AD remitters and responders to either continue on SPRAVATO plus AD or to switch to placebo nasal spray plus oral AD. Stable remission was defined as a MADRS score  $\leq 12$  for at least three of the last four weeks prior to randomization. Stable response was defined as  $\geq 50\%$  decrease in MADRS total score from baseline in each of the last two weeks prior to randomization, but not meeting criteria for stable remission. The primary efficacy endpoint was time to relapse among stable remitters during the maintenance phase. Relapse was defined as MADRS total score  $\geq 22$  for 2 consecutive assessments separated by 5 to 15 days or hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or any other clinically relevant event suggestive of relapse (as assessed by a Relapse Adjudication Committee).

#### *Study Population*

Inclusion criteria: male or female 18 to 64 years of age, inclusive, with recurrent or single episode ( $\geq 2$  years) MDD (per DSM-5 criteria) without psychotic features, as established using clinical assessment, and confirmed by the Mini-International Neuropsychiatric Interview (MINI); having an IDS-C30 total score of  $\geq 34$  and total score  $\geq 28$  on the MADRS (remote, independent rater), consistent with moderate-to-severe depression; and having TRD, defined as nonresponse ( $\leq 25\%$  improvement) to  $\geq 2$  but  $\leq 5$  oral antidepressant treatments taken at adequate dosage and duration for the current episode of depression assessed by the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ).

**Exclusion criteria: Previous nonresponse of depressive symptoms to ESK or ketamine in the current major depressive episode (MDE), to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current MDE, or nonresponse to an adequate course of treatment with electroconvulsive therapy (ECT) in the current MDE; received vagal nerve stimulation (VNS) or deep brain stimulation (DBS) in the current episode of depression; had a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with**

**psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive compulsive disorder (OCD), intellectual disability, or personality disorder; having homicidal ideation/intent (per investigator's clinical judgment), or suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS); or history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.**

## *Results*

### Baseline Characteristics

Of the 705 patients who enrolled, 437 entered directly into the study and the other patients transferred from one of two short-term ESK studies (fixed dose, n=150; flexible dose, n=118). The treatment groups of stable remitters (n=176) and stable responders (n=121) were comparable based on demographic and clinical characteristics. For all enrolled patients at baseline of the induction phase, the mean age was 46.1 years, 64.8% were female, 90.1% were white and the mean age when diagnosed with MDD was 32.7 years.

### Efficacy

**Primary Endpoint: Among stable remitters, 26.7% of patients in the ESK+AD group and 45.3% of patients in the AD+PBO group experienced a relapse event during the maintenance phase.** Stable remitters in the ESK + AD group were 51% less likely to relapse versus those in the AD + PBO group. The median time to relapse (95% CI) was not estimable (NE) for the ESK+AD group as the 50% relapse rate was not reached based on Kaplan–Meier estimates. The median time to relapse was 273.0 (97.0; NE) days for the AD+PBO group ([Figure: Kaplan-Meier Estimates of Patients Who Remained Relapse-Free - Stable Remitters](#)).

### Safety

**No new safety concerns were observed in this long-term study with repeated weekly or every other weekly dosing of SPRAVATO + AD. The majority of adverse events (AEs) were mild to moderate, observed post dose on dosing days, and generally resolved in the same day** ([Table: Adverse Events Reported ≥10% in Either Treatment Group During Maintenance Phase](#)).

Event, n (%)	ESK + AD n = 152	AD + PBO n = 145
Dysgeusia	41 (27.0)	10 (6.9)
Vertigo	38 (25.0)	8 (5.5)
Dissociation	35 (23.0)	0
Somnolence	32 (21.1)	3 (2.1)
Dizziness	31 (20.4)	7 (4.8)
Headache	27 (17.8)	14 (9.7)
Nausea	25 (16.4)	1 (0.7)
Vision blurred	24 (15.8)	1 (0.7)
Hypoesthesia oral	20 (13.2)	0

### **Intranasal ketamine**

#### ***Lapidus et al., 2014***

**In a randomized, double-blind, cross-over, proof of concept trial, Lapidus et al. studied intranasal ketamine in adults (age 21-65) with depression.** Participants had to have failed at least one prior antidepressant (AD) trial in the current episode and were allowed to continue stable doses of psychotropics (including AD) throughout the study. Inclusion criteria included a diagnosis of Major Depressive Disorder (MDD), chronic or recurrent, without psychotic features and a baseline score  $\geq 30$  on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C). Exclusion criteria included the following: unstable medical/neurological condition, axis I disorder other than MDD, high risk of suicide, substance abuse/dependence in past 6 months, psychotic disorder, bipolar disorder, developmental disorder, lifetime abuse/dependence on ketamine/phencyclidine.

**The study consisted of two seven-day treatment periods; treatment periods were at least seven days apart. To progress from the first to the second treatment period, participants had to have an IDS-C score  $\geq 24$ . An anesthesiologist in a clinical research unit provided the 20 minute administration of either 50 mg of racemic ketamine hydrochloride or placebo (0.9% saline solution). Study drug or placebo was provided in identical syringes, containing clear solutions of either 100 mg/ml ketamine in 0.9% saline or saline**

**alone. An LMA MADgic mucosal atomization device (LMA North America, Inc., San Diego, CA) was used to provide 5 intranasal applications of solution (volume 100 µl), separated by five minutes. Each of five ketamine applications provided 10 mg of study drug.**

Vital signs (heart rate, blood pressure, respiration, and pulse oximetry) were continuously monitored for at least four hours in the research unit following treatment. In the original protocol, participants remained in the research unit overnight but after safety was shown, the protocol was changed to allow for discharge four hours after treatment with outpatient follow-up.

**The primary outcome was change in the Montgomery-Asberg Depression Rating Scale (MADRS) at 24 hours following intervention.**

In each treatment period, assessments occurred at +40 min, +120 min, +240 min, +24 h, + 48 h, +72 h, and +7 days following treatment administration. Secondary outcomes included change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) and Hamilton Anxiety Rating Scale (HAM-A) and the proportion of participants meeting response ( $\geq 50\%$  decrease in MADRS from baseline) or remission ( $\text{MADRS} \leq 9$ ) criteria.

Safety and tolerability were evaluated using the following instruments: Brief Psychiatric Rating Scale-Positive sub-scale (BPRS+), Clinician-Administered Dissociative States Scale (CADSS), mood item of the Young Mania Rating Scale (YMRS), Systematic Assessment for Treatment Emergent Effects (SAFTEE). Clinically significant changes were defined as systolic or diastolic blood pressure  $> 180/100$  mmHg or heart rate  $> 110$  beats/minute. Management of adverse effects was provided per protocol or as believed necessary by the treating anesthesiologist.

Twenty individuals qualified for the study and were randomized to one of two treatment orders: ketamine-placebo or placebo-ketamine. Two participants withdrew consent and did not participate in both treatment periods. Thus, 18 patients completed both treatment periods and were included in the modified intent to treat (mITT) sample.

Table One summarizes demographic and clinical characteristics of the study participants.

Characteristic	Value
Participants treated, n (%)	20 (100)
Gender (M/F)	10/10

Characteristic	Value
<b>Age at enrollment (yrs)</b>	48.0 $\pm$ 12.8
<b>Race (%)</b>	
<i>Caucasian</i>	18/20 (90)
<i>Asian</i>	1/20 (5)
<i>Black</i>	0/20 (0)
<i>Other</i>	1/20 (5)
<b>Hispanic (%)</b>	3/20 (15)
<b>Married (%)</b>	6/20 (30)
<b>Employed (%)</b>	10/20 (50)
<b>Age of Onset</b>	21.4 $\pm$ 12.0
<b>Illness Duration in Years</b>	27.4 $\pm$ 13.7
<b>Length of Current Episode in Years</b>	15.2 $\pm$ 17.4
<b>Failed Antidepressant Medications</b>	4.1 $\pm$ 3.9
<b>History of ECT (%)</b>	4/20 (20)
<b>History of Psychotherapy (%)</b>	17/19 (89)
<b>History of Suicide Attempts (%)</b>	2/20 (10)
<b>Past Substance Use Disorder (%)</b>	3/20 (15)
<b>Current Anxiety Disorder (%)</b>	4/20 (20)
<b>Melancholic (%)</b>	9/20 (45)
<b>Atypical (%)</b>	2/20 (10)
<b>Baseline IDS-C (Screen)</b>	<b>42.7 <math>\pm</math> 8.5</b>

*Results* Compared to placebo, ketamine administration was associated with significant improvement of depressive symptoms at the 24 hour post-intervention time point. The estimated mean difference in MADRS score was  $7.6 \pm 3.7$  (95% CI: 3.9-11.3). Response was defined as a 50% drop in MADRS score. **Twenty-four hours after ketamine administration, 8/18 (44%) of participants responded; 24 hours after placebo**

**administration, 1/18 (6%) responded. Improvement in depressive symptoms was not sustained and there was no significant difference at 72 hours or seven days.** With regard to secondary outcomes, ketamine administration was associated with significant improvement on the QIDS-SR and HAM-A at the 24-hour time point. Mean difference in QIDS-SR was  $3.0 \pm 2.4$  (95% CI: 1.1-4.9). Mean difference in HAM-A was  $4.5 \pm 3.2$  (95% CI: 1.4-7.6).

Intranasal ketamine was associated with small increases on measures of psychosis (BPRS+) and dissociation (CADSS). No relationship was found between antidepressant response and ketamine associated changes in dissociative or psychotomimetic symptoms. Four participants experienced treatment-emergent increases in systolic blood-pressure  $> 130$  mm Hg following ketamine compared to three following placebo. No patients had a diastolic blood pressure  $> 100$  mm Hg. All hemodynamic changes resolved four hours post infusion and there was no association between antidepressant response and hemodynamic changes. The most common adverse events related to ketamine administration were feeling strange/unreal, poor memory, weakness/fatigue. **There were no serious adverse events and most resolved within four hours.**

## **CONCLUSION**

SPRAVATO's approval has been a long-awaited event in the pharmacotherapy of depression. It's exciting to have an antidepressant agent that works fast and may improve suicidal ideation (Canuso et al., 2018). However, its use has significant downsides including lack of long-term effectiveness and safety data, the potential for the development of ketamine use disorder, and cost. As described above, Lapidus et al. (2014) studied intranasal racemic ketamine in adults with depression. The acquisition cost of ketamine solution would undoubtedly be less than that of SPRAVATO but the study only lasted seven days and compounding/administering the final product outside of a research setting would be problematic.

## **RECOMMENDATION**

SPRAVATO should be added to the formulary with restrictions.

## **References**

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**April 5, 2019**